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Seminar for physicians
Seminar za lekare u praksi
UDK 616.98:578.834]-036
https://doi.org/10.2298/MPNS2304117G

CORONAVIRUS - CLINICAL MANIFESTATIONS BY ORGAN SYSTEMS AND PROGNOSIS

KORONAVIRUS – KLINIČKE MANIFESTACIJE PO ORGANSKIM SISTEMIMA I PROGNOZA

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Summary

Introduction. Coronaviruses were first isolated in 1962, and they belong to the family Coronaviridae, subfamily Orthocoronavirinae. Coronavirus disease 2019 is a complex multisystem disease that affects all organ systems. **Respiratory Manifestations**. Coronavirus disease 2019 pneumonia may present with fever, weakness, malaise, tachypnea and dyspnea. Acute respiratory distress syndrome is the most severe form of lung damage, manifested by pronounced respiratory insufficiency that requires oxygen therapy. **Cardiovascular Disorders**. The most common clinical presentations of coronavirus disease 2019 infection are: acute coronary syndrome - myocardial infarction, arrhythmias, myocarditis, myopericarditis, pericardial effusion, and thromboembolic complications. **Neurological Disorders**. The most common neurological symptom is headache, which is caused by activation of the trigeminal nerve endings due to the coronavirus infection. The severe forms of the disease are associated with ageusia, anosmia, and disorders of consciousness, concentration problems, and encephalopathy. **Renal Disorders**. The coronavirus infection affects all kidney structures with preferential tropism for glomerular cells. There are two types of kidney damage; mild and severe form requiring hemodialysis. **Skin Changes**. Skin changes appear due to coagulation disorders and inflammation of the walls of small blood vessels. **Ophthalmic Manifestations**. The most important ophthalmic manifestation is follicular conjunctivitis, which may appear in the early and late stages of the disease. **Conclusion**. The prognosis of coronavirus disease 2019 depends on the involvement of organ systems, the age of the patient, associated comorbidities, and the time of treatment initiation.

Key words: COVID-19; Coronavirus Infections; Diagnosis; Signs and Symptoms; Prognosis; Risk Factors; Severe Acute Respiratory Syndrome; Cardiovascular Diseases

Sažetak

Uvod. Koronavirusi su prvi put izolovani 1962. godine, pripadaju porodici *Coronavirinae* potfamiliji *Orthocoronavirinae*. Koronavirus je kompleksna multisistemska bolest koja ostavlja posledice na sve organske sisteme. **Respiratorne menifestacije.** U sklopu COVID pneumonije prisutni su: povišena temperatura, slabost, malaksalost, anosmija, ageuzija, tahipnea i dispnea. Akutni respiratorni distres sindrom predstavlja najteži oblik oštećenja pluća, manifestuje se izraženom respiratornom insuficijencijom koja zahteva visoku potporu kiseonikom. **Kardiovaskularni poremećaji.** Najčešće kliničke prezentacije koronavirusne infekcije su: akutni koronarni sindrom − infarkt miokarda, aritmije, miokarditis, mioperikarditis, perikardna efuzija i tromboembolijske komplikacije. **Neurološki poremećaji.** Najčešći neurološki simptom je glavobolja koja nastaje aktivacijom završetaka trigeminalnog nerva usled infekcije koronavirusom. Kod težih formi bolesti prisutni su: ageuzije, anosmija, poremećaj svesti, koncentracija i encefalopatija. **Bubrežni poremećaji.** Uticaj koronavirusne infekcije registrovan je u svim bubrežnim strukturama sa predominantnim tropizmom prema glomerulskim ćelijama. Postoje dva tipa bubrežnog oštećenja − blaga i teška forma koja zahteva hemodijalizu. **Promene na koži.** Kožne promene se pojavljuju zbog poremećaja koagulacije i inflamacije zida malih krvnih sudova. **Oftalmološke manifestacije.** Najznačajnija oftalmološka manifestacija je folikularni konjuktivitis koji se može pojaviti u ranoj i kasnoj fazi bolesti. **Zaključak.** Prognoza bolesti zavisi od reperkusija na organske sisteme koronavirusne infekcije, starosti bolesnika, pridruženih komorbiditeta i momenta započinjanja lečenja.

Ključne reči: COVID-19; infekcije korona virusom; dijagnoza; znaci i simptomi; prognoza; faktori rizika; akutni respiratorni sindrom; kardiovaskularna oboljenja

Introduction

Coronaviruses were first isolated in 1962, and have been shown to cause disease in mammals and birds [1]. Under the electron microscope, they have the shape of a crown due to the presence of glycoproteins on the viral surface. They are positive-strand ribonucleic acid chains which belong to the family of Coronaviridae, subfamily Orthocoronavirinae. There are 7 types of coronaviruses that infect humans [2].

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Abbreviations

SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
COVID-19	– coronavirus disease 2019
ARDS	– acute respiratory distress syndrome
ACE-2	– angiotensin-converting enzyme
PaO_2	– partial pressure of oxygen in arterial blood
FiO_2	– fraction of inspired oxygen concentration
PEEP	– positive end-expiratory pressure
TLM	– Time/Lymphocyte Percentage Model
LYM	– Lymphocyte%

In December 2019, in the province of Wuhan in the city of Hubei, China, cases of pneumonia of unknown etiology appeared, and on January 7, it was confirmed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was the cause of the disease [3]. It is a new strain of the virus that has been identified for the first time in the human population. In genetic structure, it is similar to SARS-CoV [4].

Coronavirus disease 2019 (COVID-19) is a global health problem. It is a complex multisystem disease. The SARS-CoV-2 attacks host cells by binding to its spike glycoprotein (S) metallopeptidase called angiotensin-converting enzyme (ACE-2). The ACE-2 is present in various tissues of the body, namely in the oral and nasal mucosa, nasopharynx, lungs, kidneys, brain, heart, liver, spleen, stomach, small intestine, colon, lymph nodes, thymus, and bone marrow [5]. These receptors are present in alveolar epithelial cells of the lungs, as well as endothelial muscle cells of arteries and veins. The immune response of the infected host is intense, leading to the hyperinflammatory syndrome "cytokine storm", which is characterized by an increase in proinflammatory cytokines such as tumor necrosis factor alpha, interleukin-6 and chemokine [5, 6]. The infection manifests itself in various forms: from mild asymptomatic to severe life threatening, accompanied by respiratory failure, sepsis and multiorgan dysfunction. Risk factors for the development of a severe form of the disease are: age, associated cardiovascular, pulmonary, neurological, renal comorbidities, malignancies and various immunodeficiency states. This disease affects all organ systems.

Respiratory Manifestations

The most common symptoms of this disease include fever, weakness, malaise, anosmia, ageusia, cough, tachypnea and dyspnea [7]. These symptoms are present in coronavirus pneumonia. It is a viral interstitial pneumonia that can be further complicated as a bacterial superinfection.

Acute respiratory distress syndrome (ARDS) is the most severe form of lung damage caused by SARS-CoV-2 infection, manifested by severe respiratory failure requiring oxygen therapy [8]. It is an acute, diffuse, inflammatory damage to the lungs that leads to increased vascular permeability, increased lung weight and loss of the ventilatory part of the lung parenchyma **(Figure 1)**. The clinical picture includes hypoxemia, radiographic bilateral pulmonary patchy shadows, mixing of arterial and venous blood (shunting), increase in dead space, and decrease in pulmonary compliance. It is characterized by diffuse alveolar damage that occurs due to damage to the endothelium of alveolar capillaries and due to damage to the alveolar epithelium [8, 9].

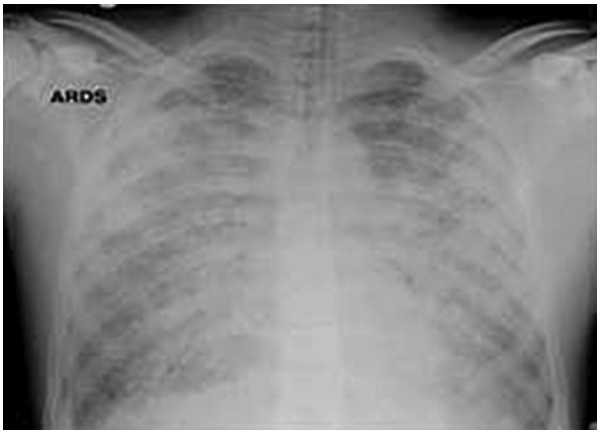

Figure 1. Acute respiratory distress syndrome - chest X-ray
Slika 1. *Akutni respiratorni distress sindrom – radiografski prikaz*

The COVID-19-related ARDS is divided into three categories:

1. Mild ARDS 200 mmHg < (ratio of partial pressure of oxygen in arterial blood - PaO_2 to the fraction of inspired oxygen concentration - FiO_2) PaO_2/FiO_2 < 300 mmHg (for positive end-expiratory pressure - PEEP > 5 cmH_2O);
2. Moderate ARDS 100 mmHg < PaO_2/FiO_2 < 200 mHg (for PEEP > 5 cm H_2O);
3. Severe ARDS PaO_2/FiO_2 < 100 mmHg (for PEEP > 5 cmH_2O).

Neutrophils and platelets that accumulate in the pulmonary capillaries play a major role in endothelial damage. Reduced pulmonary blood flow allows these cells to adhere to endothelial cells and start acting on each other [9]. Various particles are released from damaged endothelial cells, and the blood coagulation system, quinine and other inflammatory factors are activated. Complement activation attracts other inflammatory cells, so the process of alveolar-capillary membrane damage continues in autocatalytic manner and can hardly be interrupted [10, 11].

Damage to alveolar cells occurs due to inflammatory mediators, which leads to increased permeability of the alveolar-capillary membrane; transudation of plasma into alveoli causes non-cardiogenic pulmonary edema [11]. Fibrin polymerization occurs on the surface of alveoli and turns into microscopically visible deposits, the so-called hyaline membranes. The COVID-19 damages type I and type II pneumocytes. Damage to type I pneumocytes causes a decrease in respiratory area-hypoxia, while damage to type II pneumocytes reduces the production of surfactant with consequent atelectasis. These changes reduce respiratory lung capacity. Diffuse alveolar damage is divided into three phases: exudative, proliferative, and fibrous phase [11].

The exudative phase lasts several days and is characterized by airless lungs, with interstitial and alveolar edema, after which formation of hyaline membranes that line the surface of the alveolar septa occurs. The exudative phase is accompanied by a high mortality rate.

The proliferative phase lasts from one to three weeks and granulocyte tissue is present in the lung parenchyma. The fibrous phase is present between the third and fourth week. Lung tissue is diffusely fibrous.

Clinically, ARDS is manifested by dyspnea and refractory hypoxemia; the mortality rate is high, between 30 - 40%. Patients with associated comorbidities have a worse prognosis [12].

Cardiovascular Disorders

During COVID-19 infection, direct and indirect cardiovascular disorders are possible. Direct infection of cardiomyocytes, pericytes and fibroblasts induces myocardial damage with cardiotoxic effects. Due to hypoxia, microvascular damage of coronary blood vessels, endothelial cell infection and diffuse inflammation occur. The most common clinical presentations of COVID-19 infection are: acute coronary syndrome (myocardial infarction), arrhythmias (supraventricular arrhythmias, ventricular tachycardia and fibrillation, impulse conduction disorders), heart failure accompanied by systolic dysfunction, myocarditis, myopericarditis, pericardial effusion, and thromboembolic complications [12, 13]. Cardiovascular consequences occur most often in the advanced phase of the disease, in patients with a greater need for oxygen support and the progression of radiological findings. Early recognition is important in order to positively influence the outcome of the disease [13].

Coronavirus affects hypercoagulability with a prevalence of 25 - 43%. Elevated levels of fibrinogen and D-dimer are laboratory indicators of coagulation disorders, with discretely prolonged prothrombin time and partial thromboplastin time, while platelet count is slightly elevated or decreased [13]. These coagulation disorders occur in the complex interaction of vascular endothelial damage directly caused by infection or indirectly by inflammatory mediators. Hypercoagulability is responsible for the expression of tissue factor under the influence of activated mononuclear cells and interleukin-6 as well as direct viral infection of endothelial cells with the release of plasminogen activators and von Willebrand factor multimers [14]. A study conducted in Amsterdam proved that the usual prophylaxis of deep vein thrombosis did not affect the formation of micro thrombi during the COVID-19 infection [14, 15].

Neurological Disorders

Coronaviruses may have a neuroinvasive potential that, in addition to anosmia caused by olfactory bulb damage, ageusia, feelings of instability and disorders in concentration, can cause impaired consciousness (epileptic attack and delirium) in severe forms of the disease. Encephalopathy, which is present in the severely ill, is a consequence of the action of cytokines [16, 17].

The most common symptom is headache caused by activation of trigeminal nerve endings due to direct infection with coronavirus or indirectly through circulating proinflammatory cytokines, due to hypoxia and vasculopathy. The headache is usually bilateral, localized frontally, temporo-parieto-occipital or periorbital, pulsating in character, with poor response to analgesics [17].

Renal Dysfunction

The COVID-19 infection affects all kidney structures with preferential tropism for glomerular cells. Mild to severe renal impairment requires hemodialysis [17]. Renal damage with respiratory deterioration accompanied by radiological progression and increased need for oxygen support is a predictor of lethal outcome. In a Spanish study of 36 patients with renal insufficiency requiring hemodialysis, 30.5% were fatal [18].

Skin Changes

The most common skin changes appear in the distal parts of the toes in the form of erythematous or livid macules, plaques and nodules. They occur due to coagulation disorders and inflammation of the small blood vessel walls. These changes are not indicators of the severity of the disease, they most often occur in mild forms [17]. There are also changes in the form of vesicles and pustules on an erythematous base. Vesicles appear in the early phase of the disease before the onset of symptoms or around the third day and they are usually localized on the trunk. Painful erosions and ulcerations, erythematous changes and aphthous ulcers appear on the mucosa, with the possible appearance of extensive changes in the form of gingivitis [18] **(Figure 2).**

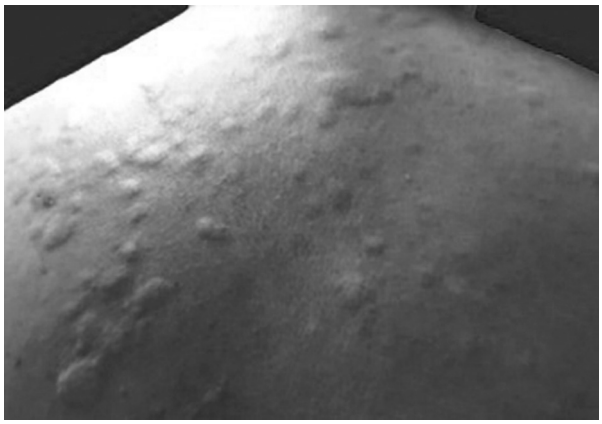

Figure 2. Skin changes in COVID-19 infection
Slika 2. *Promene na koži u COVID-19 – infekciji*

Ophthalmic Manifestations

The most important ophthalmic manifestation in COVID-19 infection is follicular conjunctivitis, which may occur in the early and late stages of the disease. In most cases, it is bilateral, accompanied by redness, conjunctival hyperemia, chemosis, epiphora and in-

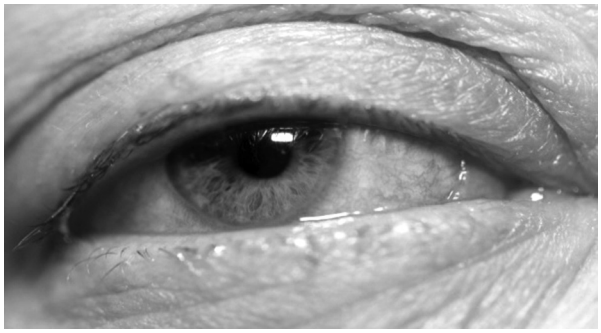

Figure 3. Conjunctivitis in COVID-19 infection
Slika 3. *Konjuktivitis u COVID infekciji*

crease in tear secretion. In some patients, there are changes in the retinal ganglion cells which cause permanent visual impairment [19] **(Figure 3)**.

Prognosis

In severe forms of the disease, the prognosis is poor, accompanied by a high mortality rate up to 60% [20].

Unfavorable prognosis indicators:

- Age ≥ 65, men.
- Associated diseases: heart disease (including arterial hypertension), lung disease, diabetes, malignant disease, immunosuppression.
- Laboratory findings: severe lymphopenia, elevated troponin, urea, creatinine, lactate dehydrogenase, C-reactive protein, and D-dimer.

In Italy, the Time/Lymphocyte Percentage Model (TLM) is also used, i.e. lymphopenia is an effective and valuable indicator for determining the severity of the disease in hospitalized patients with COVID-19. The TLM is based on the fact that patients have different percentages of lymphocytes after the onset of COVID-19 infection [20].

The TLM-1 (Time Lymphocyte% (LYM) Model), 10 to 12 days after the onset of symptoms, patients with LYM > 20% are initially classified as 'moderately severe' and are cured relatively quickly. Patients with LYM < 20% should initially be classified as 'severe cases' [21].

The TLM-2 (Time Lymphocyte% Model), approximately 17 - 19 days after the onset of symptoms, patients with LYM > 20% are recovering, 5% < LYM < 20% are still at risk and need attention, LYM < 5% are critical cases, with a high mortality rate and the need for treatment in intensive care units [22].

Lethal outcomes caused by COVID-19 infection

- 53% respiratory failure
- 33% concomitant respiratory and heart failur
- 7% heart failure.

The recovery depends on the age, comorbidities and the severity of the clinical picture. Recovery from a mild infection takes up to two weeks, while more severe forms of the disease take three to six weeks. Symptoms such as fatigue, coughing, and difficulty returning to daily activities may persist for a long period of time after illness. Recovery of lung and respiratory function in patients with a mild form of the disease occurs within six months of the onset of the first symptoms. In patients with a more severe form of the disease who require hospitalization but not admission to intensive care unit, recovery is established within 12 months [23]. In patients with the most severe form of the disease, who require mechanical ventilation during hospitalization, pulmonary manifestations persist in the form of restrictive lung disease, decreased pulmonary diffusion capacity and fibrosis, which directly affects the quality of life [24].

Conclusion

The prognosis of coronavirus disease 2019 depends on the involvement of organ systems, the patient's age, associated comorbidities, and the time of initiation of therapy. It is very important to know the clinical manifestations of this disease well, because timely recognition and treatment reduce the possibility of complications and more severe forms of the disease. The recovery is individual, depending on the age, comorbidities and severity of the clinical picture.

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Rad je primljen 9. XI 2022.
Recenziran 27. II 2023.
Prihvaćen za štampu 27. II 2023.
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